MATHEMATICAL MODELS OF BONE REMODELING AND NUMERICAL SIMULATIONS ON CAD SYSTEMS (Free Boundary Problems)

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ABSTRACT

Bone remodeling is metabolism of the bone through repetition of the resorption by osteoclasts and formation by osteoblasts. Osteoblasts produce inorganic calcium phosphate which is converted to hydroxyapatite and organic matrix consisting mainly of type I collagen, and then deposit new bone to the part of the bone resorped by osteoclasts. Osteoclasts dissociate calcium by secreting acid and degradate organic components by releasing lysosomal enzymes. Moreover, osteocytes in the bone play an important role in sensing various physical loads and conveying signals to activate osteoblasts. These three kinds of cells are linked to each other and perform the bone remodeling. Appropriate parameters representing the states of the bone and marrow are introduced and a mathematical model describing the bone remodeling phenomena is presented. The model involves an interface equation which determines the surface of the bone, and our approach leads us to a new type of free boundary problems. Results of numerical simulations on a CAD system are visualized and then compared to *in vivo* data.

KEYWORDS

mathematical model of bone remodeling, interface equation of Hamilton-Jacobi type, convective reaction-diffusion system, numerical simulations on CAD systems, free boundary problem.

1 Introduction

This paper is concerned with mathematical modeling of processes and dynamics of the bone remodeling phenomena and numerical simulations via the mathematical model. The study of bone remodeling is important from the point of view of medical studies in bone diseases such as osteoporosis, physiological studies in internal architecture of

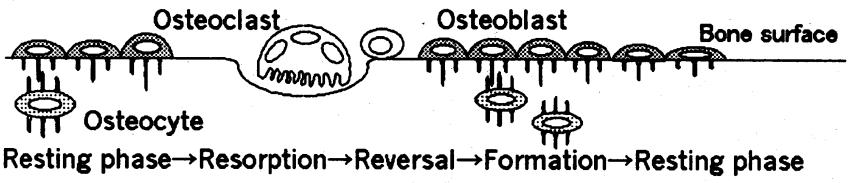
the bones and optimal design of dental implants. So far, intensive researches have been made in the related fields. Here it should be emphasized that mathematical models in conjunction with numerical simulations provide us with a reasonable approach to combine and systematize the knowledge concerning bone remodeling phenomena which has been obtained so far.

Our aim is outlined as follows. First we give a mathematical description of the bone remodeling phenomena and make an attempt to investigate the processes and dynamics through computer simulations. These complex processes and dynamics are governed by various principles. Biophysical phase transition processes of calcium are taken into account. Secondly, we introduce a PDE model and formulate a free boundary problem for a specific convection reaction-diffusion system in a fixed universal domain Ω. A feature of our argument here is to formulate the free boundary condition in terms of an interface equation of Hamilton-Jacobi type in Ω. Thirdly, our main purpose of this paper is to present a discrete mathematical model in which time-dependent subdomains of Ω, $\Omega(t)$, are determined to represent the varying bone surface. In this model four parameters A, B, C and W are employed to represent the concentration of calcium, cell density of osteoblasts, cell density of osteoclasts and an order parameter, respectively. The order parameter W takes its values in $[-1, 1]$ and is supposed to characterize three phases of calcium: calcium ions in the marrow, calcium contained in osteoid and that in the bone. The concentration A of calcium in the bone is understood to be a saturation rate A_0. Here on the boundaly $\Gamma(t)$ of each $\Omega(t)$ we impose 0-Neumann boundary conditions for A, B, C and W. The free boundary $\Gamma(t)$ is defined as the 0-level set of a solution of the interface equation in the universal set Ω. It is interesting to investigate the approximation-solvability of the free boundary problem. Finally, results of computer simulations are compared to *in vivo* data. In these numerical simulations, the following four points are taken into account: First, effective methods for visualization are necessary to present the results. Secondly, precise bone data are extremely difficult to obtain in a usual way and it is necessary to choosing reasonable coefficients and scale of parameters by taking available bone data into the model under consideration. Thirdly, it is required to check the reliability of the model and computation. Fourthly, it is important to check cosistency with the real phenomena.

2 Bone remodeling phenomena

In the bone remodeling processes three kinds of cells play a crucial role. Observations by microscopes suggest that bone surface is smooth and have no sharp corners. Osteoclasts dissociate calcium by secreting acid and degradate organic components by releasing lysosomal enzymes. Osteoblasts produce inorganic calcium phosphate which is converted to hydroxyapatite and then form osteoid with organic matrix consisting mainly of type I collagen. Osteoid is mineralized to deposit new bone to the part of the bone resorped by osteoclasts. Osteoblasts are then taken into the new bone and become osteocytes. Osteocytes are living in the bone and play an important role in sensing physical loads and chemical stimuli and in conveying the signals to activate osteoblasts. Bone remodeling is metabolism of the bone through repetition of the resorption by osteoclasts and formation

by osteoblasts. The process may be decomposed into five phases as depicted below:



Various stimuli affect these cells and calcium. Stress-strain distribution in the bone may be described in terms of Maxwell's stress tensors and generates piezoelectricity $\phi \equiv \phi(t,x)$. Such piezoelectricity provides time-dependent electric fields $\mathbf{E} = -\nabla\phi$ which propagate in the marrow. Stress-strain distribution in the bone also generate interstitial fluid flow. Osteocytes are connected to each other through the capillary sized tubes and sense interstitial fluid flows. These biomechanical stimuli as well as pressure are sensed by osteocytes. Osteocytes convey these information to cytokines in the marrow which are local enzymes and cytokines convey the biomechanical stimuli to osteoblasts as well as osteoclasts.

3 Mathematical description – A PDE model–

In order to formulate a mathematical model describing the bone remodeling phenomena, we introduce the four parameters $A \equiv A(t,x)$, $B \equiv B(t,x)$, $C \equiv C(t,x)$ and $W \equiv W(t,x)$ in the following way: First, we fix a universal domain $\Omega \subset \mathbb{R}^3$ in which the bone remodeling is supposed to take place and denote by $\Omega(t)$ a portion of Ω which represents the marrow at time t. In other words, $\Omega(t)$ stands for the domain of the bone remodeling at time t. Next, the parameter A represents the concentration of calcium at location $x \in \Omega$ and time t. Here it is assumed that $A(t,x) \equiv A_0$ (the satulation rate) on $\Omega - \Omega(t)$. The parameters B and C stands for the cell densities of osteoblasts and osteoclasts at location $x \in \Omega(t)$ and time t, respectively. The order parameter W takes its values in $[-1,1]$ and represents the three phases of calcium in the sense that A means the concentration of calcium ions in the marrow $\Omega(t)$ if $W(t,x) = 1$, the concentration of calcium on the bone surface or in osteoid if $-1 < W(t,x) < 1$, and $A(t,x) = A_0$ if $W(t,x) = -1$. The constraint that $W(t,x) \in [-1,1]$ for $t \geq 0$ may be formulated by using the subdifferential operator $\partial I_{[-1,1]}(\cdot)$ in the real line $\mathbb{R}$ of the indicator function $I_{[-1,1]}(\cdot)$ of $[-1,1]$.

The motion of the bone surface is determined by means of a Lipschitz continuous function $u \equiv u(t,x)$ on Ω such that for $t \geq 0$, $u(t,x) \in [-1,1]$, $u(t,x) = 1$ in an interior of $\Omega(t)$, $u(t,x) = -1$ in an interior of $\Omega - \Omega(t)$, and the boundary $\Gamma(t)$ of $\Omega(t)$ is defined as the outside boundary of the 0-level set $\{x \in \Omega : u(t,x) = 0\}$. Now the outward normal $\nu \equiv \nu(t,x)$ to $\Gamma(t)$ is given by $u_t/|\nabla u|$ provided that $\Gamma(t)$ is smooth. Hence it is natural to determine the function u as a viscosity solution of the evolution equation of Hamilton-Jacobi type

$$u_t = V|\nabla u|, \qquad t \geq 0, \quad x \in \Omega, \tag{1}$$

where $V \equiv V(t,x)$ stands for the velocity of motion in the direction of $\nu(t,x)$ of the boundary $\Gamma(t)$ at x. By means of the parameters introduced above, the state of the

inside of the marrow may be described as follows: First, the diffusion effects on the concentration of calcium, cell densities of osteoblasts and osteoclasts, and the phase transition of calcium are represented by $d_A\Delta A$, $d_B\Delta B$, $d_C\Delta C$ and $d_W\Delta W$, where d_A, d_B, d_C, d_W are diffusion coefficients and Δ is the Laplace operator on $\Omega(t)$ subject to the 0-Neumann boundary condition. Secondly, the advection effects on A, B and C along the negative and positive directions of physical or chemical stimulation $\boldsymbol{E} \equiv \boldsymbol{E}(t,x)$ at (t,x) may be represented as $-e_A\nabla\cdot(\boldsymbol{E}A)$, $-e_B\nabla\cdot(\boldsymbol{E}B)$, and $e_C\nabla\cdot(\boldsymbol{E}C)$, respectively, where $\boldsymbol{E}$ is understood to be a time-dependent vector field, e_A, e_B and e_C are advection coefficients and ∇ stands for the spacial nabla. Likewise, $a_B\nabla(B\nabla A)$ means the advection effect on calcium ions along the gradient of the concentration of A.

The effect on the reliese of calcium by osteoclasts and the mineralization of calcium by osteoblasts may be expressed as $\gamma CA - \beta BA$ for some positive coefficients β and γ in an appropriate sense. The effects on the decrease and increase of calcium, osteoblasts and osteoclasts in accordance with the level at (t,x) of a physical or chemical potential $\phi \equiv \phi(t,x)$ are represented as $-c_A\phi A$, $-c_B\phi B$ and $c_C\phi C$, respectively. Osteoblasts and osteoclasts are linked through the coupleing described below, although they do not share the same location. This property may be represented as $-\kappa_B CB$ and $-\kappa_C BC$ for appropriate coefficients κ_B and κ_C.

Using these mathematical representations, we formulate the following PDE model in a noncylindrical domain $\cup_{t\geq 0}(\{t\}\times\Omega(t))$:

$$A_t = d_A\Delta A - e_A\boldsymbol{E}\cdot\nabla A + \gamma CA - \beta BA - c_A\phi A, \tag{2}$$

$$B_t = d_B\Delta B - e_B\boldsymbol{E}\cdot\nabla B + a_B\nabla B\cdot\nabla A + \varepsilon_B\frac{A}{A_{00}+A}A_0B - c_B\phi B - \kappa_B CB, \tag{3}$$

$$C_t = d_C\Delta C + e_C\boldsymbol{E}\cdot\nabla C - a_C\nabla C\cdot\nabla A + \varepsilon_c\left(1-\frac{A}{A_{00}+A}\right)A_0C + c_C\phi C - \kappa_C BC, \tag{4}$$

$$W_t \in d_W\Delta W + \sigma_B B - \sigma_C C + \partial I_{[-1,1]}(W) \tag{5}$$

together with the interface equation (1) with the velocity of motion V defined by

$$V = \eta Z,\ Z = \sigma_B B - \sigma_C C, \tag{6}$$

where $\eta \equiv \eta(t,x)$ denotes the rate of formation or the rate of resorption each of which is specified in accordance with the values of Z.

Equation (5) describes the time evolution of the phase transition of calcium in the marrow. The order parameter W increase on the part of higher cell density of osteoblasts and decreases on the part of higher cell density of osteoclasts. It is assumed that bone formation is motivated on the part where W attains 1, while that bone resorption is initialized on the part where W reaches -1. Our model does not contain any parameter representing the cell densities of osteocytes, although the role of osteocytes is indirectly described in terms of coupling of osteoblasts and osteoclasts. Bone formation leads new

osteocytes. Osteocytes convey signals to osteoclasts via osteoblasts and the activated osteoclasts perform bone resorption which increase the concentration of calcium ions in the marrow. The high concentration of calcium then motivate bone formation. In this way, the bone remodeling takes place and this linkage is called the coupling of osteoblasts and osteoclasts. Our model involves four diffusion operators defined on the time-dependent domain $\Omega(t)$. We here impose the homogeneous Neumann boundary conditions for A, B, C and W on the boundary $\Gamma(t)$ at each time t. Finally, it is a characteristic feature of our argument that the bone surface $\Gamma(t)$ is determined as the outside boundary of the 0-level set of a solution u of the interface equation (1).

4 Discrete mathematical model

In accordance with the mathematical description of bone remodeling phenomena, we here present a discrete mathematical model for the bone remodeling. Our model is formulated in the form of a finite difference scheme for discretized parameters associated, respectively, with A, B, C and W.

First, we fix a suitably chosen positive number l in order to represent a spce differencing. We then choose the universal domain Ω to be a sufficiently large rectangle $[0,a] \times [0,b]$ and define a discretization Ω_l of Ω by means of grid points (il, jl), $i = 0, 1, \ldots, 2M$, $j = 0, 1, \ldots, 2N$, in Ω such that $2Ml = a$ and $2Nl = b$. In order to make stable computation subject to the homogeneous Neumann boundary conditions, we employ so-called four-point-cell grid generation. Namely, for each pair (i,j) with $0 \leq i \leq M-1$ and $0 \leq j \leq N-1$, we consider a cell $(i,j)^*$ which consists of the four points $(2i, 2j)$, $(2i+1, 2j)$, $(2i, 2j+1)$ and $(2i+1, 2j+1)$ so that Ω_l is subdivided into $M \times N$ subdomains $l(i,j)^*$ of Ω_l consisting of the four points $(2il, 2jl)$, $((2i+1)l, 2jl)$, $(2il, (2j+1)l)$ and $((2i+1)l, (2j+1)l)$. We then define a coarser discretization Ω_l^* of Ω, that is defined by means of the $M \times N$ subdomains $l(i,j)^*$, and call each subdomain a *position* in Ω_l^*, instead of a grid point.

Secondly, we choose a positive number h to discretize the time variable t in the sense that t is approximated by nh. The ratio l^2/h is remained to be a constract δ so that the so-called CFL condition for the difference scheme introduced below may be satisfied. The mesh ratio δ must be chosen in accordance with the norms of the coefficients and parameters.

In the universal set Ω_l of grid points, we define a discretization Ω_l^n of $\Omega(nh)$ which represents the approximatate marrow at time $t = nh$. To this end, we first formulate a discrete interface equation on Ω_l^* as a difference scheme

$$u_{i,j}^{n+1} = \overline{u}_{i,j}^n + hV_{i,j}^n g_{i,j}^n, \quad i = 0, 1, \ldots, M, j = 0, 1, \ldots, N, \tag{7}$$

which is consistent with the interface equation (1). Here $u_{i,j}^n$ is a value defined on the position $l(i,j)^*$ and Ω_l^* is considered the union of positions $l(i,j)^*$ for which $u_{i,j}^n \geq 0$. Also, $\overline{u}_{i,j}^n$ is defined as a weighted mean of $u_{i,j}^n$ and its four adjacent values such as

$$\overline{u}_{i,j}^n = \varepsilon(u_{i+1,j}^n + u_{i-1,j}^n + u_{i,j+1}^n + u_{i,j-1}^n) + (1-\varepsilon)u_{i,j}^n.$$

In particular, the standard Lax-Friedrichs scheme is obtained by choosing suitable weights. Now the discretization Ω_l^n and its boundary Γ_l^n are both considered unions

of subdomains $l(i,j)^*$. Hence at each time nh and position $l(i,j)^* \subset \Gamma_l^n$, we define the outward normal $\nu_{i,j}^n$ to Γ_l^n as one of the four vectors $(1,0)$, $(0,1)$, $(-1,0)$ and $(0,-1)$. The values $V_{i,j}^n$ stand for the velocity of motion of $\Gamma_{i,j}^n$ in the direction of $\nu_{i,j}^n$ and the values $g_{i,j}^n$ approximatate $|\nabla u|$ in (1) at positions $l(i,j)^*$ in Ω_l^* and are defined by

$$g_{i,j}^n = (\max(D_{x,-2l}u^n, 0)^2 + \min(D_{x,2l}u^n, 0)^2 + \max(D_{y,-2l}u^n, 0)^2 + \min(D_{y,2l}u^n, 0)^2)^{1/2}.$$

We write $A_{i,j}^n, B_{i,j}^n, C_{i,j}^n$ and $W_{i,j}^n$ for the approximate values of A, B, C and W at time nh and point (il, jl) and define the associated functions A^n, B^n, C^n and W^n on $h\overline{\mathbb{N}} \times \Omega_l$, where $h\overline{\mathbb{N}} = \{nh : n = 0, 1, \ldots\}$. We also define $A_{(i,j)^*}^n$ to be the arithmetic mean of the four numbers $A_{p,q}^n$, $(p,q) \in (i,j)^*$. Likewise, the arithmetic means $B_{(i,j)^*}^n$, $C_{(i,j)^*}^n$ and $D_{(i,j)^*}^n$ are defined.

In order to define the difference operators Δ_l and ∇_l associated with the Laplacian Δ and special nabla ∇, we employ the translation operators $\tau_{x,l}$ and $\tau_{y,l}$ defined by

$$\tau_{x,l}A_{i,j}^n = A_{i+1,j}^n,\ \tau_{y,l}A_{i,j}^n = A_{i,j+1}^n,\ \tau_{x,-l}A_{i,j}^n = A_{i-1,j}^n,\ \tau_{y,-l}A_{i,j}^n = A_{i,j-1}^n.$$

The defference operators Δ_l and ∇_l are then defined, respectively, by

$$\Delta_l = l^{-2}(\tau_{x,l} + \tau_{y,l} - 4I + \tau_{x,-l} + \tau_{y,-l}), \quad \nabla_l = [l^{-1}(\tau_{x,l} - \tau_{x,-l}), l^{-1}(\tau_{y,l} - \tau_{y,-l})].$$

Moreover, we write $\boldsymbol{E}_{ij}^n$, ϕ_{ij}^n, σ_B^n and σ_C^n for the approximate values of $\boldsymbol{E}$, ϕ, σ_B and σ_C at time nh and grid point $(il, jl) \in \Omega_l$.

Our mathematical model is formulated as follows:

$$\begin{aligned} h^{-1}\left(A_{i,j}^{n+1} - A_{i,j}^n\right) &= d_A\Delta_l A_{i,j}^n - e_A\nabla_l \cdot (\mathbf{E}_{i,j}^n A^n) \\ &+ \gamma C_{i,j}^n A_{i,j}^n - \beta B_{i,j}^n A_{i,j}^n - c_A\phi_{i,j}^n A_{i,j}^n \end{aligned} \tag{8}$$

$$\begin{aligned} h^{-1}\left(B_{i,j}^{n+1} - B_{i,j}^n\right) &= d_B\Delta_l B_{i,j}^n - e_B\nabla_l \cdot (\mathbf{E}_{i,j}^n B_{i,j}^n) + a_B\nabla_l \cdot (B_{i,j}^n \nabla_l A_{i,j}^n) \\ &+ \varepsilon_B \frac{A_{i,j}^n}{A_{00} + A_{i,j}^n} A_0 B_{i,j}^n - c_B\phi_{i,j}^n B_{i,j}^n - \kappa_B C_{i,j}^n B_{i,j}^n \end{aligned} \tag{9}$$

$$\begin{aligned} h^{-1}\left(C_{i,j}^{n+1} - C_{i,j}^n\right) &= d_C\Delta_l C_{i,j}^n + e_C\nabla_l \cdot (\mathbf{E}_{i,j}^n C_{i,j}^n) - a_C\nabla_l \cdot (C_{i,j}^n \nabla_l A_{i,j}^n) \\ &+ \varepsilon_C \left(1 - \frac{A_{i,j}^n}{A_{00} + A_{i,j}^n}\right) C_{i,j}^n + c_C\phi_{i,j}^n C_{i,j}^n - \kappa_C B_{i,j}^n C_{i,j}^n \end{aligned} \tag{10}$$

$$h^{-1}\left(W_{i,j}^{n+1} - W_{i,j}^n\right) = d_W\Delta_l W_{i,j}^n + \sigma_B^n B_{i,j}^n - \sigma_C^n C_{i,j}^n \tag{11}$$

$$V_{i,j}^n = \eta_{i,j}^n Z_{i,j}^n, \quad Z_{i,j}^n = \sigma_B^n B_{(i,j)^*}^n - \sigma_C^n C_{(i,j)^*}^n. \tag{12}$$

in addition to the interface equation (7), where $\eta_{i,j}^n$ means the rate of formation if $\eta_{i,j}^n > 0$ and $W_{(i,j)^*}^n = 1$ and $\eta_{i,j}^n$ means the rate of resorption if $\eta_{i,j}^n > 0$ and $W_{(i,j)^*}^n = -1$. Likewise, $\eta_{i,j}^n = 0$ means that no remodeling processes take place at the position $l(i,j)^* \subset \Gamma_l^n$. Finally, we impose the following conditions on the functions A^n, B^n, C^n and W^n which correspond to the 0-Neumann boundary conditions for A, B, C amd W

at time $t = nh$: If for instance $\nu^n_{i,j} = (1,0)$, then $u^n_{i+1,j} < 0$ and $u^n_{i,j} \geq 0$. In this case $l(i+1,j)^*$ is adjacent to but outside Ω^*_l and the following identities are assumed to hold:

$$A_{(i+1,j)^*} = A_{(i,j)^*},\ B_{(i+1,j)^*} = B_{(i,j)^*},\ C_{(i+1,j)^*} = C_{(i,j)^*},\ W_{(i+1,j)^*} = W_{(i,j)^*}. \tag{13}$$

Equations (13) in the other cases are formulated in the same way.

5 Algorithm for computer simulation

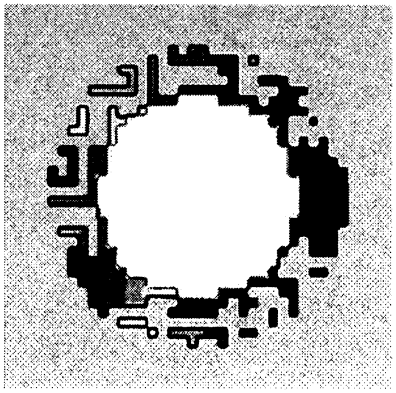
In this section we discuss an algorithm for computer simulation based on our model. First, we set up the domain of bone remodeling by specifying the coefficients contained in the model. In order to establish our model on a computer, we employ the method of four-point-cell grid generation. A pair of computable numbers l and h is chosen so that the CFL-condition may hold and a rectangler universal domain Ω_l of grid points is constructed. We then fix a subdomain Ω^0_l of Ω_l to represent the marrow at time $0h$ and a circle S in the interior of Ω^0_l to express the portion occupied by a dental implant. The boundary Γ^0_l of Ω^0_l is then specified as explained in the previous section. In this way, the initial horizontal section of the marrow in which a dental implant has been installed is represented in the discretized domain Ω_l.

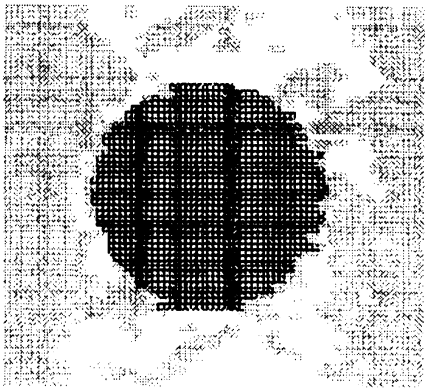
Secondly, equations (7) through (13) are used to find the free boundary Γ^n_l and determine the values of parameters A^n, B^n, C^n and W^n on Ω^n_l for each $n \in \overline{\mathbb{N}} = \{0,1,2,\ldots\}$. Suppose that the domain Ω^n_l and the values of functions A^n, B^n, C^n and W^n on Ω^n_l are known. In accordance with the values of W^n on the boundary Γ^n_l, the values of η^n are determined and equation (7) is applied to compute the values of u^{n+1} on Ω^n_l. Now the domain Ω^{n+1}_l in the $(n+1)$th step is determined as follows:

Suppose for instance that $l(i,j)^* \subset \Gamma^n_l$ and $\nu^n_{i,j} = (1,0)$. Hence $l(i+1,j)^* \cap \Omega^n_l = \emptyset$, $u^n_{i-1,j} = 1$, $u^n_{i,j} = 0$ and $u^n_{i+1,j} = -1$. First we consider the case in which $W^n_{i,j} = -1$. Then, in view of the boundary condition (13), the value $u^{n+1}_{i+1,j}$ is obtained by computing $u^{n+1}_{i+1,j} = u^n_{i+1,j} + hV^n_{i,j}g^n_{i,j}$. If $\eta^n_{i,j} > 0$, $u^n_{i,j} = 1$ and $u^{n+1}_{i+1,j} = 0$, then the subdomain $l(i+1,j)^*$ is remained to be outside but adjacent to Ω^n_l. Otherwise, the subdomain $l(i+1,j)^*$ is not added to Ω^n_l. This means that the bone in $l(i+1,j)^*$ is resorped provided that $u^n_{i,j} = 1$ and $u^n_{i+1,j} = 0$. We next consider the case in which $W^n_{i,j} = 1$. Then an imaginary value $\hat{u}^{n+1}_{i-1,j}$ is computed by $\hat{u}^{n+1}_{i-1,j} = u^n_{i-1,j} + h\eta^n_{i,j}Z^n_{i,j}g^n_{i,j}$. If $u^{n+1}_{i,j} = -1$ and $\hat{u}^{n+1}_{i-1,j} = 0$, then the subdomain $l(i,j)^*$ is removed from Ω^n_l. Otherwise, the subdomain $l(i,j)^*$ is remained in Ω^{n+1}_l. This means that a new bone is formed on $l(i,j)^*$ provided that $\hat{u}^{n+1}_{i-1,j} = 0$ and $u^{n+1}_{i,j} = -1$. In this way, Ω^{n+1}_l is constructed in a finite step of computation. The other cases can be treated in the same way.

6 Numerical results and comparison with *in vivo* data

A discrete scheme consistent with the PDE model is formulated by an appropriate choice of the mesh ratio $\delta \equiv h/l^2$ and applied to perform computer simulations. The numerical results agree with *in vivo* bone data in a qualitative way.





The left figure shows a form of the bone obtained by the computation and the right figure depicts a horizontal section of bone structure supporting a cylindrical dental implant.

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